

13. (Amended) The oligonucleotide conjugate according to claim 1, wherein the oligonucleotide is partially complementary to the nucleic acid coding for the proto-oncogene bcl-2.

14. (Amended) The oligonucleotide conjugate according to claim 13, which comprises the nucleic sequence 5' -GTT CTC CCA GCG TGT GCC AT-3' (SEQ ID NO: 1).

15. (Amended) The oligonucleotide conjugate according to claim 1, wherein the oligonucleotide is a peptide nucleic acid derivative (PNA).

16. (Amended) The pharmaceutical preparation, containing the oligonucleotide conjugate according to claim 1, in combination with a pharmaceutically compatible carrier.

17. (Amended) A method of antisense therapy, comprising administering the oligonucleotide defined according to claim 1 to a host in need of treatment.

18. (Amended) The method according to claim 17 wherein said treatment is cancer treatment, viral disease treatment, inflammatory process treatment, asthmatic disease treatment, central nervous system disease treatment and cardiovascular disease treatment.

REMARKS

Turning now to the substance of the Office Action, the Examiner made objections to certain formalities and cited art against the instant claims.

I. Regarding the objections, as stated in the Office Action, Claims 4-18 stand objected as being in improper form; i.e., improper multiple dependent claims.

In addition to the objection under 37 C.F.R. 1.75(c), claims 17 and 18 also stand objected because the claims were deemed indefinite due to an alleged failure to set forth positive process steps.

The last objection is directed to claim 14 for disclosing a nucleotide sequence in the absence of a sequence listing.

The objection is traversed for the following reasons.

The claims have been reworded to address the multiple dependency issue and to place the claims in a form more acceptable under U.S. practice.

The CRF and paper copy of the Sequence Listing will be filed shortly.

Thus, on the filing of the Sequence Listing, the objection can be removed.

II. The Examiner asserted that claims 1-3 are obvious in view of Nagy et al., in view of Lu et al. and Taylor et al.

Nagy et al. allegedly teach somatostatin analogs conjugated to doxorubicin.

Lu et al. allegedly teach complexing an antisense DNA for a molecule preferentially bound in the liver for targeting of the DNA to the liver.

Taylor et al. was alleged to teach antisense oligonucleotides and modifications thereof and thereto.

The rejection is traversed for the following reasons.

The conjugates of the present invention permit antisense therapy in tumors and particularly tumors in which somatostatin receptors (SSTRs) are overexpressed. The achievement of the present invention to transport antisense molecules selectively into tumor cells which overexpress the respective tumor-selective receptor was not obvious in view of the cited references.

First, Nagy et al. teach the delivery of a small molecule, i.e. doxorubicin (molecular weight 580), into the target cell. Nagy et al. lack any guidance on the delivery of substantially larger compounds such as the oligonucleotides of the present application. Moreover, there is no expectation in Nagy et al. that a molecule larger than doxorubicin could be internalized via the SSTR. Nagy et al. do not indicate how the coupling of a large molecule, i.e. oligonucleotide having a weight >5000Da, to the relatively small somatostatin analog (1500Da) will affect the mechanism of action of endocytosis. In particular, a person skilled in the art will assume that the at least 5-times larger oligonucleotide will seriously weaken the affinity of the somatostatin analog to the SSTR. Moreover, the passing of large molecules, in particular charged molecules such as oligonucleotides, through a cell membrane is a quite complex process which is difficult to predict. In view of the failures of numerous targeting concepts in the art, Nagy et al. do not form a promising starting point for developing an oligonucleotide conjugate. A person skilled in the art could not consider SSTRs as suitable targets for oligonucleotides, because only the transport of small molecules via this system has been reported.

Second, a person skilled in the art would not combine the teachings of Nagy et al. and Lu et al. to replace cytotoxins with oligonucleotides.

Lu et al. do not deal with the transport of compounds into tumors. Lu et al. teach the delivery of antisense DNA not normal cells. The characteristics of normal tissues fundamentally differ from that of cancerous tissues. Hence, a person skilled in the art would not consider Lu et al. for developing a tumor-selective delivery system for cancerous tissues.

Further, Lu et al. teach the specific delivery of antisense DNA into liver cells. Liver cells do not carry SSTRs, the targets of somatostatin analogs. A liver-specific delivery of a substance is a completely different type of problem than a tumor-specific delivery. Thus, a person skilled in the art would not consider Lu et al. for applying conjugates with somatostatin analogs.

Moreover, Lu et al. teach a conjugate having an ionic bond between a cationic asialoglycoprotein and an anionic 67-mer antisense DNA, whereas the conjugates of the present invention are covalently bonded.

Consequently, the combination of the teachings of Nagy et al. and Lu et al. would not result in the present invention, because, for example Lu et al. teach to link the oligonucleotide with the target peptide by an ionic bond.

Further, because Lu et al. report a good cellular uptake rate of the oligonucleotides and do not indicate that the intracellular stability of the oligonucleotides is inadequate, a person skilled in the art would not have been motivated to further modify the oligonucleotides taught by Lu et al.

Third, a person skilled in the art would not combine the teachings of Nagy et al. with Lu et al. and Taylor et al. to incorporate phosphorothioate modifications into the antisense molecules of Lu et al.

While Taylor et al. teach that modified antisense oligomers can be applied in cancer therapy, Taylor et al. do not suggest delivering the antisense oligomer via receptor-mediated endocytosis into the cell. Taylor et al. teach transfection by a cationic lipid, microinjection and electroporation (page 565, 2nd para). As Taylor et al. do not propose to couple the antisense oligomer to a target peptide for receptor-mediated endocytosis, a person skilled in the art would not consider Taylor et al. for modifying the specific target system of Lu et al.

Finally, the fact that antisense DNAs were known in the art does not give a person skilled in the art a reasonable expectation of success in formulating conjugates comprising an antisense oligonucleotide and a somatostatin analog, because a successful uptake of oligonucleotides was extremely unpredictable in view of the chemical and physical characteristics of polynucleotide-oligomers and the countless failures in the development of diverse targeting concepts for the specific uptake of oligonucleotides. Surprisingly, the inventors found out that both the targeting to the receptor as well as internalizing of the oligonucleotides can be achieved with the claimed conjugates, despite the characteristics of the oligonucleotides. In fact, the inventors succeeded for the first time in receptor-mediated delivering antisense oligonucleotides into a tumor cell which overexpresses the respective receptor.

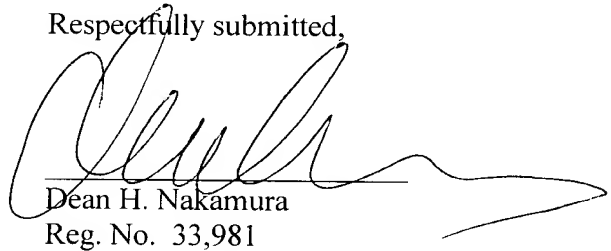
In view thereof, a prima facie use of obviousness has not been made. Moreover, the invention provides unexpected and superior properties. Thus, the rejection can be removed.

CONCLUSION

Applicant has taken substantial steps to advance prosecution. Reexamination, reconsideration, withdrawal of the objection and rejection and early indication of allowance are requested respectfully. If any questions remain, the Examiner is urged respectfully to contact the undersigned at the local exchange provided below.

The Commissioner hereby is authorized to charge payment of any fees under 37 C.F.R. § 1.17 that may become due in connection with the instant application or credit any overpayment to Deposit Account No. 18-2220.

Respectfully submitted,



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Marked-Up Claims
for
09/781,980

4. (Amended) The oligonucleotide conjugate according to claim 1[, 2 or 3], wherein the 3' end in the oligonucleotide is covalently bonded to a propanediol group.
5. (Amended) The oligonucleotide conjugate according to [any one of] claim[s] 1 [to 4], wherein the somatostatin analog is octreotide or octreotate, or a derivative thereof.
6. (Amended) The oligonucleotide conjugate according to [any one of] claim[s] 1 [to 5], wherein the somatostatin analog is covalently bonded to the 5' end of the oligonucleotide molecule.
7. (Amended) The oligonucleotide conjugate according to [any one of] claim[s] 1 [to 6], wherein the somatostatin analog is covalently bonded to a base present in the oligonucleotide molecule via a spacer.
9. (Amended) The oligonucleotide conjugate according to [any one of] claim[s] 1 [to 8], wherein the intracellular nucleic acid sequence is an mRNA or viral RNA.
11. (Amended) The oligonucleotide conjugate according to [any one of] claim[s] 1 [to 10], wherein the oligonucleotide has a length of 8 to 50 nucleotides.

Marked-Up Claims
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13. (Amended) The oligonucleotide conjugate according to [any one of] claim[s] 1 [to 12], wherein the oligonucleotide is partially complementary to the nucleic acid coding for the proto-oncogene bcl-2.

14. (Amended) The oligonucleotide conjugate according to claim 13, which comprises the nucleic sequence 5' -GTT CTC CCA GCG TGT GCC AT-3' (SEQ ID NO: 1).

15. (Amended) The oligonucleotide conjugate according to [any one of] claim[s] 1 [to 13], wherein the oligonucleotide is a peptide nucleic acid derivative (PNA).

16. (Amended) The pharmaceutical preparation, containing the oligonucleotide conjugate according to [any one of] claim[s] 1 [to 15], optionally in combination with a pharmaceutically compatible carrier.

17. (Amended) [Use] A method of antisense therapy, comprising administering the oligonucleotide defined according to [any one of] claim[s] 1 [to 15 for the antisense therapy] to a host in need of treatment.

18. (Amended) [Use] The method according to claim 17, wherein said treatment is [for] cancer treatment, [for treating] viral disease[s] treatment, [for treating] inflammatory process[es] treatment, [for treating] asthmatic disease[s] treatment, [for the therapy of

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diseases of the] central nervous system disease treatment and [for the therapy of]
cardiovascular disease treatment.